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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/594,908	01/08/2009	Xiangbin Wang	11774-006-999	3643

20583 7590 02/03/2011

JONES DAY
222 EAST 41ST ST
NEW YORK, NY 10017

EXAMINER	
HALVORSON, MARK	
ART UNIT	PAPER NUMBER
1642	
MAIL DATE	DELIVERY MODE
02/03/2011	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/594,908	WANG ET AL.	
	Examiner	Art Unit	
	Mark Halvorson	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 November 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *21-40* is/are pending in the application.

4a) Of the above claim(s) *34-40* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *29 September 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The Art Unit and Examiner of your application in the USPTO have changed. To aid in correlating any papers in this application, all further correspondence regarding this application should be directed to Art Unit 1642, Mark Halvorson.

Claims 21-40 are pending.

Election/Restrictions

Applicant's election without traverse of Group I, claims 21-33 in the reply filed on November 24, 2010 is acknowledged. Applicant's election without traverse of the species, the single chain tri-specific antibody of SEQ ID NO:4 is acknowledged.

Claims 34-40 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Claims 21-33 are under examination.

Specification

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth below.

A sequence in Fig 3 is not identified by a SEQ ID NO. Inserting the SEQ ID NO. of the sequence in the description of Fig 3 in the Brief Description of the Drawings would obviate this objection.

In response to this office action, Applicant must comply with the sequence rules, 37 CFR 1.821 - 1.825. Failure to comply with these requirements will result in ABANDONMENT of the application under 37 CFR 1.821(g). Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a). In no case may an applicant extend the period for reply beyond the SIX MONTH statutory period. The nature of the non-compliance did not preclude an

examination of the elected invention on the merits, the results of which are presented below.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 21-31 and 33 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a single chain tri-specific antibody comprising an anti-tumor associated antigen antibody or antigen binding fragment thereof, an anti-CD3 antibody or antigen binding fragment thererof and an anti-CD28 antibody or antigen binding fragment therof, does not reasonably provide enablement for a single chain tri-specific antibody comprising an anti-tumor associated antigen antibody fragment, an anti-CD3 antibody fragment and an anti-CD28 antibody fragment. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The claims are drawn to a single chain tri-specific antibody comprising an anti-tumor associated antigen antibody fragment, an anti-CD3 antibody and an anti-CD28 antibody fragment.

It is interpreted that an antibody fragment does not necessarily comprise the antigen binding portion of the antibody. The specification does not disclose any guidance or working examples on how to use an antibody fragment that does not comprise the antigen binding fragment of the antibody.

One cannot extrapolate the teaching of the specification to the scope of the claims because the specification does not provide examples or guidance on how to detect the of protein expression of SEQ ID NO:2 using a fragment of an antibody that does not comprise the antigen binding fragment of the antibody.

The state of the prior art is such that it is well established in the art that the formation of an intact antigen-binding site of antibodies routinely requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs or hypervariable regions, which provide the majority of the contact residues for the binding of the antibody to its target epitope (Paul, Fundamental Immunology, 3rd Edition, 1993, pp. 292-295, under the heading "Fv Structure and Diversity in Three Dimensions"). The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity, which is characteristic of the immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites (Paul, page 293, first column, lines 3-8 and line 31 to column 2, line 9 and lines 27-30). Thus, it would be impossible for a skilled artisan to construct a tri-specific antibody comprising an anti-tumor associated antigen antibody fragment that does not comprise the complete antigen-binding fragment, an anti-CD3 antibody fragment that does not comprise the complete antigen binding fragment and an anti-CD28 antibody fragment that does not comprise the complete antigen binding fragment.

Given the disclosure of the specification and the teaching in the art that indicates the unpredictability of treating cancer and autoimmune disease, one skilled in the art could not predictably make a functional tri-specific antibody comprising an anti-tumor associated antigen antibody fragment that does not comprise the complete antigen-binding fragment, an anti-CD3 antibody fragment that does not comprise the complete antigen binding fragment and an anti-CD28 antibody fragment that does not comprise the complete antigen binding fragment. Therefore, in view of the breadth of the claims, lack of guidance in the specification, the absence of working examples, and

the state of the art, it would require undue experimentation for one skilled in the art to practice the invention as broadly claimed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 21-24, 26, 28-31 and 33 are rejected under 35 U.S.C. 102(b) as being anticipated by Song e al (Acta Biochimica Biophysica Sinica, 2003, 35:503-510).

The claims are drawn to a single chain tri-specific antibody comprising in tandem an anti-tumor associated antigen antibody fragment, a first interlinker, an anti-CD3 antibody fragment, a second interlinker and an anti-CD28 antibody fragment.

Song et al discloses a single chain tri-specific antibody comprising in tandem an anti-tumor associated antigen antibody fragment, a first interlinker, an anti-CD3 antibody fragment, a second interlinker and an anti-CD28 antibody fragment. (paragraph 1.2) Song et al's single chain tri-specific antibody comprises a C myc tag (paragraph 1.3) and two interlinkers, an interlinker-Fc and an interlinker-HSA. (paragraph 2.1).

Claims 21-24, 26, 28-31 and 33 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 02/83738, (published 10 April 2002) as evidenced by the national stage application US Patent Application Publication 2005/0175606, published 11 August 2005).

The claims are drawn to a single chain tri-specific antibody comprising in tandem an anti-tumor associated antigen antibody fragment, a first interlinker, an anti-CD3 antibody fragment, a second interlinker and an anti-CD28 antibody fragment.

Song et al discloses a single chain tri-specific antibody comprising in tandem an anti-tumor associated antigen antibody fragment, a first interlinker, an anti-CD3 antibody fragment, a second interlinker and an anti-CD28 antibody fragment. (claims 1, 5). Song et al's single chain tri-specific antibody comprises a C myc tag (paragraph 91, see sequence comparison below) and two interlinkers, an interlinker-Fc and an interlinker-HSA. (claim 6, see sequence comparisons below).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 21-26, 28-31 and 33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Song e al (Acta Biochimica Biophysica Sinica, 2003, 35:503-510, cited previously) in view of Holliger et al (Cancer Res, 1999, 59:2909-2916).

The claims are drawn to a single chain tri-specific antibody comprising in tandem an anti-tumor associated antigen antibody fragment, a first interlinker, an anti-CD3 antibody fragment, a second interlinker and an anti-CD28 antibody fragment, wherein the anti-tumor associated antigen is CEA.

Song et al has been described supra.

Song et al does not disclose a single chain tri-specific antibody comprising in tandem an anti-CEA antibody fragment, a first interlinker, an anti-CD3 antibody fragment a second interlinker and an anti-CD28 antibody fragment.

Holliger disclose two bispecific antibodies, an anti CEA X anti-CD3 antibody and an anti-CEA X B7 fusion protein. (page 2910, 1st column).

One of ordinary skill in the art would have been motivated to apply Holliger et al's anti-CEA antigen binding antibody fragment to Song et al's single chain tri-specific antibody because Song et al disclose that the single chain tri-specific antibody could be a powerful CD3-based immunotherapy without simultaneous administration of other costimulatory molecules (page 3, 1st paragraph). Furthermore, Holliger et al disclose that CEA is a model antigen as one of the most well-characterized tumor antigens on solid tumors. (page 2915, 1st column). It would have been prima facie obvious to substitute Song et al's single chain tri-specific antibody comprising an anti-ovarian carcinoma scFv with Holliger et al's anti-CEA antigen binding antibody fragment to make a single chain tri-specific antibody comprising an anti-CEA scFv.

Claims 21- 33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Song e al (Acta Biochimica Biophysica Sinica, 2003, 35:503-510, cited previously) in view of Holliger et al (Cancer Res, 1999, 59:2909-2916, cited previously) in further view of Koga et al (Hybridoma, 1990, 9:43-56) and Robinson et al. (US Patent No. 5,618,920, issued April 8, 1997).

The claims are drawn to a single chain tri-specific antibody comprising in tandem an anti-tumor associated antigen antibody fragment, a first interlinker, an anti-CD3 antibody fragment, a second interlinker and an anti-CD28 antibody fragment, wherein the anti-tumor associated antigen is CEA.

Song et al has been described supra.

Holliger et al has been described supra.

Neither Song et al nor Holliger et al disclose an anti-CEA antigen binding fragment comprising SEQ ID NO:1.

Koga et al disclose the anti-CEA monoclonal antibody (page 44) that was used to make the anti-CEA scFv. (page 17 of the specification)

Robinson et al teach the determination of nucleic acids encoding VH and VL of any known antibody and use of said VH and VL to produce FV (see column 1-45, and columns 12-22). Robinson et al teach that "The invention also produces consensus sequences and specific oligonucleotide sequences useful as probes for hybridization and priming cDNA synthesis of any hybridoma mRNA coding for variable regions of any desired specificity." (see column 4, last paragraph). The nucleic acid constructs of the VH and VL are used to make reconstructed antibodies, such as chimeric antibodies, that prevent harmful hypersensitive reactions in humans (column 1, lines 41-43).

One of ordinary skill in the art would have been motivated to apply Robinson et al's method determination of nucleic acids encoding VH and VL of an antibody to Koga et al's anti-CEA antibody because Robinson et al states teach the determination of nucleic acids encoding VH and VL of any known antibody while Koga et al disclose that the antigen recognized by PAM-1 is present on gastric adencarcinomas. One of ordinary skill in the art would have been motivated to apply Robinson et al and Koga et al's anti-CEA antibody's VH and VL to Song et al and Holliger et al's single chain tri-specific antibody comprising an anti-CES scFv because Koga et al disclose that the anti-CEA antibody localized to tumor tissue *in vivo*. (page 51, 2nd paragraph). It would have been prima facie obvious to have substituted Song et al and Holliger et al's anti-CEA scFv with Robinson et al and Koga et al's anti-CEA antibody's VH and VL to make a functional single chain tri-specific antibody comprising an anti-CEA scFv.

```
RESULT 14
US-10-474-345-8
; Sequence 8, Application US/10474345
; Publication No. US20050175606A1
; GENERAL INFORMATION:
;  APPLICANT: Huang, Hua-Liang
;  APPLICANT:  Cheng, Ju-Long
;  APPLICANT:  Wang, Xiang-Bin
;  APPLICANT:  Song, Ling-Pin
;  APPLICANT:  Zhang, Zhong
;  APPLICANT:  Lin, Qing
;  APPLICANT:  Gu, Ying
```

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;  TITLE OF INVENTION: Cyclic Single-Chain Trispecific Antibody
;  FILE REFERENCE: L35.2I-11327-US01
;  CURRENT APPLICATION NUMBER: US/10/474,345
;  CURRENT FILING DATE:  2003-10-06
;  PRIOR APPLICATION NUMBER: PCT/CN02/00252
;  PRIOR FILING DATE: 2002-04-10
;  PRIOR APPLICATION NUMBER: CN 01110554.2
;  PRIOR FILING DATE: 2001-04-11
;  NUMBER OF SEQ ID NOS: 10
;  SOFTWARE: PatentIn version 3.2
; SEQ ID NO 8
;   LENGTH: 11
;   TYPE: PRT
;   ORGANISM: Artificial
;   FEATURE:
;   OTHER INFORMATION: Interlinker peptide between antitumor antibody,
reshaped CD3
;   OTHER INFORMATION: antibody and reshaped CD28 antibody
US-10-474-345-8

  Query Match             100.0%;  Score 53;  DB 5;  Length 11;
  Best Local Similarity   100.0%;
  Matches   11;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps
0;

Qy          1 EQKLISEEDLN 11
              ||||||||||
Db          1 EQKLISEEDLN 11



RESULT 1
US-10-474-345-6
; Sequence 6, Application US/10474345
; Publication No. US20050175606A1
; GENERAL INFORMATION:
;  APPLICANT: Huang, Hua-Liang
;  APPLICANT:  Cheng, Ju-Long
;  APPLICANT:  Wang, Xiang-Bin
;  APPLICANT:  Song, Ling-Pin
;  APPLICANT:  Zhang, Zhong
;  APPLICANT:  Lin, Qing
;  APPLICANT:  Gu, Ying
;  TITLE OF INVENTION: Cyclic Single-Chain Trispecific Antibody
;  FILE REFERENCE: L35.2I-11327-US01
;  CURRENT APPLICATION NUMBER: US/10/474,345
;  CURRENT FILING DATE:  2003-10-06
;  PRIOR APPLICATION NUMBER: PCT/CN02/00252
;  PRIOR FILING DATE: 2002-04-10
;  PRIOR APPLICATION NUMBER: CN 01110554.2
;  PRIOR FILING DATE: 2001-04-11
;  NUMBER OF SEQ ID NOS: 10
;  SOFTWARE: PatentIn version 3.2
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; SEQ ID NO 6
;   LENGTH: 26
;   TYPE: PRT
;   ORGANISM: Artificial
;   FEATURE:
;   OTHER INFORMATION: Interlinker peptide between antitumor antibody,
reshaped CD3
;   OTHER INFORMATION: antibody and reshaped CD28 antibody
US-10-474-345-6

  Query Match             100.0%;  Score 142;  DB 5;  Length 26;
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0;

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              ||||||||||||||||||||||||||
Db          1 NSTYRVVSVLTVLHQDWLNGKEYKCK 26


RESULT 1
US-10-474-345-7
; Sequence 7, Application US/10474345
; Publication No. US20050175606A1
; GENERAL INFORMATION:
;  APPLICANT: Huang, Hua-Liang
;  APPLICANT:  Cheng, Ju-Long
;  APPLICANT:  Wang, Xiang-Bin
;  APPLICANT:  Song, Ling-Pin
;  APPLICANT:  Zhang, Zhong
;  APPLICANT:  Lin, Qing
;  APPLICANT:  Gu, Ying
;  TITLE OF INVENTION: Cyclic Single-Chain Trispecific Antibody
;  FILE REFERENCE: L35.2I-11327-US01
;  CURRENT APPLICATION NUMBER: US/10/474,345
;  CURRENT FILING DATE:  2003-10-06
;  PRIOR APPLICATION NUMBER: PCT/CN02/00252
;  PRIOR FILING DATE: 2002-04-10
;  PRIOR APPLICATION NUMBER: CN 01110554.2
;  PRIOR FILING DATE: 2001-04-11
;  NUMBER OF SEQ ID NOS: 10
;  SOFTWARE: PatentIn version 3.2
; SEQ ID NO 7
;   LENGTH: 25
;   TYPE: PRT
;   ORGANISM: Artificial
;   FEATURE:
;   OTHER INFORMATION: Interlinker peptide between antitumor antibody,
reshaped CD3
;   OTHER INFORMATION: antibody and reshaped CD28 antibody
US-10-474-345-7

  Query Match             100.0%;  Score 125;  DB 5;  Length 25;
  Best Local Similarity   100.0%;
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  Matches   25;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps
0;

Qy          1 FQNALLVRYTKKVPQVSTPTPVEVS 25
              |||||||||||||||||||||||||
Db          1 FQNALLVRYTKKVPQVSTPTPVEVS 25
```

Summary

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mark Halvorson whose telephone number is (571) 272-6539. The examiner can normally be reached on Monday through Friday from 8:30am to 5 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Misook Yu, can be reached at (571) 272-0839. The fax phone number for this Art Unit is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Mark Halvorson/
Examiner, Art Unit 1642